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A QTL on 12q Influencing an Inflammation Marker and Obesity in White Women: The NHLBI Family Heart Study

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Abstract

It has been recognized that obese individuals are intrinsically in a state of chronic inflammation, as indicated by positive correlations between serum levels of C-reactive protein (CRP) and various anthropometric measures of obesity. To explore the hypothesis that a gene(s) may underlie this relationship, we conducted bivariate linkage analyses of BMI and CRP in white and African-American (AA) families of the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study (FHS). Variance components linkage analysis as implemented in SOLAR was performed in 1,825 whites (840 men and 985 women) and 548 AAs (199 men and 351 women). CRP exhibited significant genetic correlations with BMI in women (0.54 ± 0.10 for white and 0.53 ± 0.14 for AA) and the combined samples (0.37 ± 0.09 for white and 0.56 ± 0.13 for AA), but not in men. We detected a maximum bivariate lod score of 3.86 on chromosome 12q24.2–24.3 at 139 cM and a suggestive linkage signal (lod = 2.19) on chromosome 19p13.1 (44 cM) in white women. Both bivariate peaks were substantially higher than their respective univariate lods at the same locus for each trait. No significant lod scores were detected in AAs. Our results indicate that chromosome 12q may harbor quantitative trait loci (QTLs) jointly regulating BMI and CRP in white women.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/oby

DISCLOSURE

The authors declared no conflict of interest.

INTRODUCTION

Atherosclerosis often leads to ischemia or infarction of the heart, brain, kidney, and other organs. Obesity has been classified as one of the major risk factors for the development of atherosclerosis (1). Recent studies have also demonstrated that atherosclerosis is intrinsically a chronic inflammatory response of the vessel wall, characterized by the accumulation of leukocytes, especially macrophages and T cells (2). The concept of inflammation in relation to obesity was first reported by Hotamisligil *et al.* with a seminal publication in 1993 (ref. 3). They presented that the expression of the tumor necrosis factor-α is markedly increased in adipocytes of obese animals. It was supported by the evidence that the human adipocytes and adipose tissue constitutively express tumor necrosis factor-α, and its expression of tumor necrosis factor-α falls markedly after weight loss (4). Adipose tissue is now recognized as the second only to lymphatic tissue in the secretion of signaling molecules including the proinflammatory cytokines, such as C-reactive protein (CRP) (5). The release of the inflammatory mediators from adipose tissue in persons with excess body fat may induce chronic inflammation. CRP is a critical inflammation cytokine which can be used as a sensitive marker for systemic inflammation. In addition, it has been shown that circulating concentrations of CRP are related to the anthropometric measures of obesity (6,7). One possible explanation could be that the innate immune system shares genetic effects (pleiotropy) with obesity.

The genetic contribution to obesity has been investigated extensively in several populations. The heritability of BMI was estimated as varying from 20 to 80% (8–10). The levels of CRP were also described to be influenced by a substantial degree of genetic effect. The relative contribution of additive genetic variance to baseline CRP was estimated as 40% in whites (11), which agrees with another report by Vickers *et al.* (12). Higher heritability of CRP (46%) was observed in American Indians (13), while a lower estimation (20%) was observed in a study for the elderly twins (14). One study in African Americans (AAs) suggested that CRP was ~38% heritable in hypertensive sibships (15).

Although publications have demonstrated that CRP phenotypically correlated with obesity, only one publication has reported on their genetic correlation to our knowledge. A significant genetic correlation was found between CRP and BMI using 349 white families randomly recruited in the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study (FHS), a subset sample of the present study (16). In the present study, we hypothesize that there exists potential gene(s) influencing both levels of inflammation marker CRP and BMI. To test this hypothesis, we estimated genetic correlation and conducted bivariate linkage analyses by gender for BMI and CRP of all white and AA subjects genotyped in the NHLBI FHS.

METHODS AND PROCEDURES

Study population

The NHLBI FHS is a multicenter, population-based study to identify and evaluate genetic and nongenetic determinants of coronary heart disease, atherosclerosis, and cardiovascular disease risk factors. Details on the design and methods of the study have been published

(17). In brief, 1,245 families in the study had been chosen randomly (random group) or on the basis of a higher than expected risk of CAD (high-risk group) from previously established population-based cohort studies in 1994–1995. A total of 5,381 members of these families completed an extensive clinical evaluation, including a detailed medical and lifestyle history. Subjects were recruited from: Framingham, MA; Minneapolis, MN; Salt Lake City, UT; Forsyth County, NC. The majority subjects in the study are whites in this period.

In 2002–2003, 2,754 whites were selected from 511 large, informative pedigrees, of which 2,089 participants have been typed for genome-wide microsatellite markers. They were followed up in a clinical examination that included measurements of inflammation markers and anthropometry. In addition, 215 AA families (633 individuals) were also recruited in Birmingham, AL. They were previously examined by the Hypertension Epidemiology Network (HyperGEN), a multicenter study of the genetics of hypertension (18). The current analyses are based on 1,825 whites and 548 AAs who have been genotyped in the NHLBI FHS. All phenotypic data were obtained at the follow-up examination. We had excluded 264 whites and 95 AAs from the main analyses for the following reasons: (i) missing data on CRP or BMI ($n = 64$), (ii) fasting time <10 h ($n = 68$); (iii) self-reported rheumatoid arthritis or autoimmune diseases ($n = 227$). The present study included 401 sibling pairs among 840 men, 494 sibling pairs among 985 women, and 1,741 sibling pairs in combined white sample. The maximum number of sibling pairs per white family was 15 in women and men, and 45 in combined sample. In AA families, there were 52 men sibling pairs ($n = 199$), 142 women sibling pairs ($n = 351$), and 355 sibling pairs in combined sample. The maximum number per family was 21, 10, and 66, respectively. Each participant gave informed consent, and the study protocol was reviewed and approved by each of the participating institutions.

Measurements of phenotypes

Anthropometric measurements were collected with subjects wearing scrub suits. BMI was subsequently calculated as weight in kilograms divided by height in meters squared. Serum CRP was assayed at the University of Vermont with a high-sensitivity assay (BNII nephelometer (N High Sensitivity CRP; Dade Behring, Deerfield, IL)) with intra-assay coefficients of variation ranging from 2.3 to 4.4% and inter-assay coefficients of variation ranging from 2.1 to 5.7%.

Genotypes for preliminary linkage analysis

All 1,825 white subjects were typed for 402 microsatellite markers by the NHLBI FHS at the National Institutes of Health Mammalian Genotyping Service (Marshfield, WI). In addition, 613 whites enriched for coronary heart disease risk factors were typed for 243 autosomal STR markers by the Utah Molecular Genetics Laboratory. For 548 AA subjects, 389 microsatellite markers were genotyped in Human Genetics Center of University of Texas at Houston. Detailed information on all measurements, genotype data, and quality control are available on the NHLBI FHS website (https://dsgweb.wustl.edu/fhscc/). At a significance level of 0.05, we can achieve 0.80 of power to detect locus-specific heritabilities as low as ~12% using univariate linkage analysis (see Supplementary Methods and Procedures online).

Statistical methods

The logarithmic transformation was used to approximately normalize the distributions of CRP. Both CRP and BMI were then adjusted in the mean and the variance for the covariate effects of age, age^2, age^3, and the field center, retaining only the terms significant at the 5% level. The adjusted variables were finally standardized for further linkage analyses to a mean of 0 and a standard deviation (s.d.) of 1. Separate regression and standardization analysis were performed for men and women, thereby adjusting for sex. No outliers of the adjusted values were detected or excluded based on the criteria >4 s.d. from the mean and at least 1 s.d. from the nearest data point.

Genetic correlation

In the bivariate linkage model, the phenotype covariance can be decomposed into genetic and environmental components, such that

$$\rho_{Pheno}=\rho_g\sqrt{h_1^2h_2^2}+\rho_e\sqrt{(1-h_1^2)(1-h_2^2)},$$

where h_1^2 and h_2^2 are the heritabilities of trait 1 and trait 2, and ρ_g and ρ_e are the additive genetic and individual-specific environmental correlations between the two traits, respectively. In this study, the genetic correlation between CRP and BMI was estimated by gender using SOLAR 2.1.4 (http://www.sfbr.org/solar/index.html) (19).

Primary linkage analysis

The identity-by-descent matrix for each pedigree was computed by GeneHunter (version 2.0) (Whitehead Institute for Biomedical Research, Cambridge, MA) with multipoint approach (20). Bivariate linkage analyses were conducted for CRP and BMI for combined and gender specific samples utilizing maximum likelihood variance component methods implemented in the program SOLAR 2.1.2. In the bivariate linkage model in which a major locus and residual polygenic genetic effects influence two traits, the covariation of the two traits (Ω_{12}) for each pedigree is given by:

$$\Omega_{12}+=\Pi_q\rho_q\sigma_{q1}\sigma_{q2}+2\Phi\rho_g\sigma_{g1}\sigma_{g2}+\mathrm{I}\rho_e\sigma_{e1}\sigma_{e2},$$

where ρ_q, ρ_g, and ρ_e are the shared variances between the two traits due to the major gene, the residual genetic effects, and the individual-specific environmental effects, respectively. σ_q, σ_g, and σ_e, are the QTL specific genetic variance, the residual genetic variance, and individual-specific environmental variance, respectively. Π is a matrix whose elements (π_{qij}) provide the probability that individuals i and j are identity-by-descent at a quantitative trait locus which is linked to a genetic marker locus, Φ is the kinship matrix, and I is an identity matrix. The lod score of two degrees of freedom (2-d.f.) was produced by comparing likelihood for the linkage model in which p_q was estimated to the likelihood for the restricted model in which p_q was equal to 0 (ref. 20). The 2-d.f. effective bivariate LOD score is then divided by 2ln10 to convert to the 1-d.f. effective LOD score, which is equivalent to the univariate LOD score (21).

The false discovery rate was used to measure the expected proportion of false positives among the total number of rejections of the null hypothesis (22). False discovery rate was estimated using the SAS package and the *P* value adjusted for false discovery rate was denoted here by "*q*" value.

RESULTS

Table 1 presents the baseline characteristics for the participants genotyped in the NHLBI FHS and involved in the present study. The average age for whites was ~57 years in men and 58 years in women. AAs were younger with average age of 51 and 54, respectively. Men had a lower mean concentration of CRP compared to women in both races, and had higher mean BMI in whites but lower mean BMI in AAs. Higher levels of CRP and BMI were observed in AAs. The significant covariate terms in stepwise multiple regression analyses stratified by race and sex are provided in Table 2.

The heritabilities of CRP and BMI and their genetic and environmental correlations in gender specific samples are given in Table 3. In whites, BMI exhibited moderate heritabilities, which were higher than those of CRP in men, women, and the combined sample. AAs had relative high heritabilities for BMI in both gender specific samples and the combined sample, and moderate to high heritabilities for CRP. We observed significant gender effect on the genetic correlation between CRP and BMI, which was high in women (0.54 for whites and 0.53 for AAs) but low and nonsignificant in men (0.18 for whites and 0.39 for AAs). Compared to the estimates of whites, the heritabilities in AAs were generally higher but with much larger standard deviation due to the small sample size.

Univariate and bivariate LOD scores and the approximate locations of bivariate peaks ≥1.5 from genome scan of CRP and BMI were shown in Table 4. We detected a maximum bivariate LOD score of 3.86 at ~139 cM on chromosome 12 in white women ($P = 0.00003$, $q = 0.005$, near marker GATA4H01, Figure 1). Additional suggestive linkage evidence associated with CRP and BMI in white women was found at the position 44 cM on chromosome 19 with lod score of 2.19 ($P = 0.0008$, $q = 0.065$, near marker GATA66B04). Both linkage peaks were substantially higher than their respective univariate lods at the same chromosome location for each trait. Though CRP and BMI shared more genetic determines in AAs, the strongest linkage signal (LOD = 2.76) was obtained in men localized at 47 cM from p-telomere (p-ter) on chromosome 5 with nonsignificant *q* value ($P = 0.0002$, $q = 0.100$, near marker GATA7C06). A second peak was observed on chromosome 12 at the region 8 cM p-ter ($P = 0.0003$, $q = 0.10$, near marker GATA4H03). In addition, a peak in AA men with an lod score of 1.89 on chromosome 12 at 158 cM from p-ter ($P = 0.0016$, $q = 0.105$, near marker ATA29A06) located ~20 cM from the strongest signal detected on chromosome 12q24.2–24.3 in white women.

DISCUSSION

Many publications have reported genome scans on BMI or other obesity-related phenotypes with linkage signals spread overall 22 autosomal chromosomes (see 23 for review). Only a few studies have carried out a linkage analyses for CRP (11,15,24). The aim of present study

was to conduct the first bivariate genome-wide linkage analysis on BMI and CRP to identify loci linked to both traits. BMI and CRP were both found to be heritable moderately in whites, and moderately to highly in AAs. They were also genetically correlated among women and combined sample in both races, but not in men. In addition, two chromosomal loci were identified as regions of interest that may harbor genes with pleiotropic effects on BMI and CRP in white women.

In the present analysis, the most significant bivariate linkage region to BMI and CRP was found in white women at ~139 cM on chromosome 12 (LOD = 3.86, $P = 0.00003$, $q = 0.005$). This linkage signal coincides with a suggestive signal for abdominal subcutaneous fat (LOD = 2.9) from 156 white families in the Québec Family Study (25). The 1 LOD unit support interval of the signal spanned 24 cM, from 122 to 147 cM (12q24.1–12q24.3). The region has been linked to percent body fat (LOD = 4.08) and BMI (LOD = 3.57) measured by bioelectric impedance in 1,297 individuals from 260 white families (26). Two other genome scans for obesity have also identified linkage evidence within this region in AA populations. The first of these mapped percent energy from FAT to 12q24.21 (LOD = 2.9) in 313 subjects from 126 families of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study (27), and the second associated BMI with markers D12S1638 on 12q24.33 (Lod = 1.94) in 277 subjects from 59 pedigrees ascertained for probands with obstructive sleep apnea (28). One recent study reported bivariate linkage analysis for CRP and fibrinogen in hypertensive sibships (15). A region was identified at 12q24 (152 cM) with LOD of 3.43 in AAs, which is near our finding. Our present study also demonstrated suggestive evidence of linkage for BMI and CRP on chromosome 12 (LOD = 1.89, 158 cM, $P = 0.0016$, $q = 0.105$) in AA men.

A second suggestive QTL was detected in the current study among women at 44 cM on chromosome 19 (LOD = 2.19, $P = 0.0008$, $q = 0.065$). This peak overlaps with previously identified linkage QTLs for childhood obesity in white populations. A genome-wide linkage analysis conducted in 506 subjects from 115 multiplex French white families with at least one child with a BMI ≥ 95th percentile revealed evidence of linkage (LOD = 2.13) at 43.3 cM on chromosome 19 for age of adiposity rebound, which corresponds to the beginning of the second rise in childhood adiposity (29). Another genome scan for BMI conducted in 369 subjects from 89 German families with ≥2 obese children and/or adolescents, reported an LOD of 1.97 at 53 cM on this chromosome (30).

Our linkage results support the presence of loci influencing susceptibility to obesity and inflammation in white women. The 1 LOD unit support interval of the QTL on chromosome 12 (12q24.2–24.3) harbors an interesting candidate gene, AMP-activated protein kinase β-1 (*AMPK-β1*, 12q24.1), whose product is a regulatory subunit of AMPK. Activation of hypothalamic AMPK was shown to block leptin's effects on food intake and body weight (31). Recent findings also suggest that AMPK activation could influence CRP production by modulating adipocyte secretion of interleukin-6 (ref. 32). The 1.0-LOD support interval of the suggestive linkage signal on chromosome 19 (19p13.2–19q13.12) includes the resistin gene (*RETN*, 19p13.2). Resistin, an adipocyte-secreted hormone, was originally described as the link between obesity and insulin resistance (33). It also has been shown in subjects with type 2 diabetes that increased serum resistin is related to the elevated CRP (34).

A large number of published genome-wide scans support the hypothesis that chromosome 12q24 might harbor a gene increasing susceptibility to type 2 diabetes. In a study involving an extended pedigree with late-onset Type 2 diabetes, Shaw *et al.* have reported significant linkage (LOD = 3.65) on 12q24 at recombination fraction 0.0008, telomeric to marker D12S321 (ref. 35). Lindgren *et al.* reported a multipoint LOD score of 1.80 for this region, in a sample consisting of 58 Finnish families with 229 type 2 diabetes subjects (36). Linkage to type 2 diabetes on chromosome 12q24 has also been reported in the Africa America Diabetes Mellitus (AADM) Study (LOD score 1.92 at 131 cM near marker D12S2070) (ref. 37). It is well established that the relative risk of developing type 2 diabetes mellitus increases with increasing BMI. Recent studies also revealed that subclinical chromic low-grade inflammation might play an important role in the pathogenesis of insulin resistance and type 2 diabetes (38). CRP was found related to the degree of insulin resistance and the development of diabetes independent of obesity (39) and other well known risk factors, with a dose-dependent correlation (40). In addition, some antidiabetic agents have been shown to reduce the levels of CRP and other inflammatory markers in serum. Conversely, anti-inflammatory drugs have also been reported to improve glucose tolerance (41). Though the mechanism needs to be explored, our finding on chromosome 12q24 provided the further evidence for the potential link between obesity, inflammation, and type 2 diabetes demonstrated by recent epidemiological and clinical studies.

Few studies have examined sex differences for the associations between body composition and inflammatory markers. In present study, we observed considerably stronger genetic associations between CRP and BMI in women than in men. Our observation is consistent with results from the KORA Group (42). Their results showed that markers of inflammation were more strongly associated with measures of obesity in women than in men, and this was especially evident for CRP. Physiological differences might explain these findings. First, women have a higher total fat mass and larger subcutaneous fat deposits, while men have larger intra-abdominal fat deposits (43,44). Because anthropometric measures, such as BMI, predicted a smaller percentage of the total variance in intra-abdominal fat area for men than for women (44), which may in turn lead to the weaker association observed between measures of obesity and markers of inflammation in men. In addition, sex hormones could influence levels of inflammatory markers including CRP differently in men and women. In the present study, women had higher levels of CRP and lower BMI than men (Table 1).

One limitation of our study is that we did not have equal representation of AA and white individuals. Therefore, our study was underpowered to estimate the genetic correlation and detect linkage signals in AAs, particularly in gender specific groups. In addition, though we detected one region of significant linkage and one region of suggestive linkage for CRP and BMI in bivariate analysis in the present study, several challenges of genetic components underlying complex traits are existed in linkage analysis in terms of discovering genes, including locus heterogeneity, epistasis, low penetrance, variable expressivity. Even if statistically significant evidence of linkage is obtained, the region of linkage extensive is usually exceeding 10 cM and the candidate gene studies are still required to detect the causal gene or genes within this region. Recently, the genome-wide association study by genotyping single-nucleotide polymorphisms in a large population of cases and controls or

families has become a more powerful and efficient method to identify disease causative genes, especially for complex diseases.

In conclusion, we identified a genomic region 12q24.2–24.3 with significant bivariate linkage evidence for inflammatory biomarker CRP and obesity in white women. These findings not only reinforce the significant relationship between inflammation response and the development of obesity, but also reveal strong genetic evidence suggesting that common genes may influence both sets of traits. Follow-up study can be conducted by genotyping single-nucleotide polymorphisms in attractive candidate genes within these regions. The current trend is to use genome-wide association methods, which may be more powerful for identifying genes for common diseases and complex traits. The investigation can be extended to other systemic inflammatory biomarkers, such as interleukin-6 and monocyte chemoattractant protein-1, to explore additional insights into the pathogenesis of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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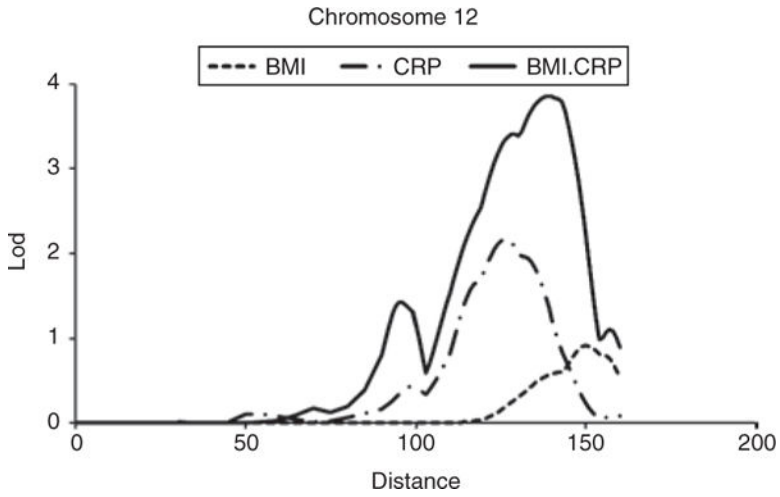

Figure 1.

Lod scores on chromosome 12 of univariate and bivariate linkage analysis for CRP and BMI in white women. CRP, C-reactive protein.

Table 1

Characteristics of the participants involved in the present linkage analysis in the National Heart, Lung, and Blood Institute Family Heart Study

	White			African American		
	Men	**Women**	**Combined**	**Men**	**Women**	**Combined**
Individuals (*n*)	840	985	1,825	199	351	548
Sibpairs (*n*)	401	494	1,741	52	142	355
Age, years	57.09 ± 13.19	58.42 ± 12.8	57.81 ± 12.98	51.48 ± 10.39	53.74 ± 11.06	52.91 ± 10.86
CRP, mg/l[a]	0.44 ± 1.00	0.79 ± 1.15	0.63 ± 1.10	0.88 ± 1.12	1.46 ± 1.17	1.25 ± 1.18
BMI, kg/m^2	29.63 ± 4.81	28.62 ± 6.24	29.09 ± 5.65	30.23 ± 6.21	34.00 ± 7.45	32.63 ± 7.25
Research center, % (*n*)						
North Carolina	17.98 (151)	23.76 (234)	21.10 (385)	1.51 (3)	2.01 (7)	1.82 (10)
Minnesota	30.48 (256)	26.40 (260)	28.27 (516)	–	–	–
Massachusetts	16.55 (139)	18.48 (182)	17.59 (321)	–	–	–
Utah	35.00 (294)	31.37 (309)	33.04 (603)	–	–	–
Alabama	–	–	–	98.49 (196)	97.99 (342)	98.18 (538)

CRP, C-reactive protein.

[a]CRP was log transformed for all participants.

Table 2

Significant covariates in regression analysis in the National Heart, Lung, and Blood Institute Family Heart Study

	White				African American			
	Men		Women		Men		Women	
	R^2	Covariates ($P < 0.05$)	R^2	Covariates ($P < 0.05$)	R^2	Covariates ($P < 0.05$)	R^2	Covariates ($P < 0.05$)
CRP	0.041	Age	0.034	Age^2, age^3, center	0.025	Center	–	–
BMI	–	–	0.048	Age^2, age^3, center	–		–	–

R^2 = proportion of the variance due to the significant covariates.

CRP, C-reactive protein.

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Table 3

Genetic correlations between CRP and BMI in the National Heart, Lung, and Blood Institute Family Heart Study

	h^2 ± s.d. (CRP)	h^2 ± s.d. (BMI)	ρ_G ± s.d. (*P* value)	ρ_E ± s.d.	ρ_{pheno}
White					
Men	0.25 ± 0.09	0.47 ± 0.09	0.18 ± 0.19 (0.384)	0.33 ± 0.09	0.27
Women	0.36 ± 0.08	0.55 ± 0.09	0.54 ± 0.10 (<0.001)	0.36 ± 0.09	0.42
Combined	0.31 ± 0.05	0.48 ± 0.05	0.37 ± 0.09 (<0.001)	0.36 ± 0.05	0.36
African American					
Men	0.41 ± 0.22	0.97 ± 0.21	0.39 ± 0.27 (0.185)	0.09 ± 1.22	0.21
Women	0.77 ± 0.14	0.72 ± 0.17	0.53 ± 0.14 (0.002)	0.03 ± 0.42	0.25
Combined	0.53 ± 0.12	0.67 ± 0.11	0.56 ± 0.13 (<0.001)	0.05 ± 0.19	0.81

CRP, C-reactive protein; h^2, heritability; ρ_E, individual-specific environmental correlation; ρ_G, additive genetic correlation; ρ_{Pheno}, phenotypic correlation.

Table 4

Bivariate lod scores and approximate locations of peaks ≥1.5 from genome scan of CRP and BMI in Family Heart Study

				Lod Scores		
Race	**Chrm**	**Locus (cM)**	**Marker**	**BMI**	**CRP**	**Bivariate (*q* value)**
White						
Men	2q36	224	GATA23D03	2.48	0.00	1.73 (0.115)
	8q22.1	139	GATA21C12	2.18	0.43	1.74 (0.115)
	15q11.2	2	AFM273YF9	2.86	0.00	1.98 (0.115)
	16p13.1	18	ATA3A07	1.07	0.13	1.63 (0.118)
Women	5q15	105	GATA3H06	2.22	0.13	1.54 (0.184)
	12q24.2	139	GATA4H01	0.58	1.36	3.86 (0.005)
	13q14	43	GATA11C08	0.95	0.01	1.93 (0.084)
	15q26	99	GATA73F01	1.32	0.00	1.58 (0.184)
	19p13.11	44	GATA66B04	1.18	0.75	2.19 (0.065)
	20p11.1	39	GATA129B03	0.94	1.21	1.56 (0.184)
Combined	2q37	260	2QTEL47	1.80	0	1.85 (0.489)
African American						
Men	1q23.3	114	GATA6A05	0.03	0.00	2.29 (0.100)
	5p13	47	GATA7C06	0.28	0.05	2.76 (0.100)
	5q33	165	GATA6E05	0.21	0.00	2.26 (0.100)
	9q34	156	AFMB303ZG9	0.23	0.22	2.42 (0.100)
	12p13	8	GATA4H03	0.00	0.00	2.54 (0.100)
	12q24.3	158	ATA29A06	0.20	0.12	1.89 (0.105)
	13p12	11	GATA23C03	2.68	0.03	2.30 (0.100)
Women	4q31.2	146	GATA107	2.45	0.17	1.83 (0.206)
Combined	16p11.2	37	AFM049XD2	1.15	0.00	1.64 (0.500)

Chrm, chromosome; cM, centimorgan; CRP, C-reactive protein; *q* value, FDR-adjusted *P* value.